To compare the effect of 'lactate-based' and 'acetate-based' intravenous fluids on the electrolytes and the acid-base status

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This is to certify that the dissertation entitled "To Compare the effect of lactate-based and acetate-based intravenous fluids on the electrolytes and the acid-base status" is a bonafide work of Dr. **Vanjare Pankaj Arvind** in partial fulfillment of the requirement for the M.D degree (Branch X) Anesthesiology Examination of The Tamil Nadu Dr. M.G.R Medical University, Chennai, to be held in February / March 2009.

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AIM

To compare the effect of lactate-based and acetate-based intravenous fluids on the electrolytes and the acid-base status, in patients undergoing major abdominal surgery.

Introduction

The choice of the intravenous fluid during surgery is often assumed to be of little significance. Isotonic crystalloid solutions are used for volume repletion during surgery, but various crystalloids can impact electrolyte and acid-base balance. Although, 0.9% (normal) saline has been used for over half a century, administration of large volumes of this fluid can lead to hyperchloremic acidosis [4,5,6,8,14,19]. This is not seen with the administration of balanced salt solutions such as Ringer lactate [3,4] or Plasmalyte 148 [4] despite having similar pH. However, intravenous administration of large amounts of Ringer lactate can increase serum lactate levels [8]. Plasmalyte A, an acetate-based balanced salt solution with a pH of 7.4, is currently available. This study is an effort to compare the effects of Plasmalyte A and Ringer lactate, on the electrolyte and acid-base status in patients undergoing major abdominal surgery.

Review of literature

Intravenous fluid administration is an important part of anesthetic management as adequate plasma volume is essential in maintaining cardiac output and tissue perfusion. Intraoperative fluid has always been a topic of debate with regard to requirement, composition and type of solution.

Fluid management strategies have undergone several swings over the past 50 years. Prior to the 60's fluid restriction was practiced during the intraoperative period. In the early 1960s it was demonstrated that major surgery was associated with significant fluid loss and these patients need large volume of peri-operative fluid. However, this was questioned by Moore and Shires [1] who suggested that trauma and surgery were associated with obligatory metabolic and endocrine response leading to retention of fluid. In the late 80s and early 90s the concept of achieving supernormal oxygen delivery ushered in the era of administering large volumes of fluid intraoperatively. However more recently the goal-directed fluid management has shown benefit in surgical settings. [16]

Similarly, there is much debate about the choice of crystalloid during surgery, some of which is not based on scientific evidence. The compositions of the various available crystalloids vary significantly and this has its implication on the homeostasis, especially after infusion of large volumes. Ringer lactate, 0.9% saline and dextrose saline are the commonly used crystalloids for peri-operative fluid maintenance and replacement. The table compares the composition of these fluids with that of Plasmalyte, a newer balanced salt solution.

	Plasma	**0.9% saline**	**Dextrose saline**	**Ringer lactate**	**Plasmalyte 148**	**Plasmalyte A**
Na mEq.L^{-1}	134-146	154	77	131	140	140
Cl mEq.L^{-1}	98-108	154	77	109	98	98
K mEq.L^{-1}	3.4-5			4	5	5
Ca mEq.L^{-1}	2.25-2.65			2.7		
Mg mEq.L^{-1}	0.7-1.1					3
Glucose mmol.L^{-1}	5-6		50			
Lactate mEq.L^{-1}	0-1			28		
Gluconate mEq.L^{-1}					23	23
Acetate mEq.L^{-1}					27	27
pH	7.3-7.4	5.6	4.0	5.5	5.5	7.4
Osmolarity mOsm.L^{-1}	280-300	308	505	309	310	294

0.9% Saline

Over the last 50 years, 0.9% (‘normal’) saline has been used for intra-operative maintenance and replacement and during other clinical conditions such as trauma and diabetic ketoacidosis. However this solution is neither ‘normal’ nor physiological (3)

0.9% saline has 9gm of NaCl dissolved in 1 liter of water. The mass of 1 mL of this solution is 1.009 gm. The molecular weight of sodium chloride is 58 $g.mole^{-1}$. Therefore, this solution contains 0.154 $mole.L^{-1}$ of NaCl which is equal to 154mE $q.L^{-1}$. Since NaCl dissociates into two ions (Na^+ and Cl^-) each is present in a concentration of 154$mEq.L^{-1}$. Since, osmolarity is equal to the number of osmotically active particles per litre, the osmolarity of 0.9% saline is 308 $mosmol.L^{-1}$.

Saline-based intravenous fluids are non-physiological in three ways. Firstly, the level of chloride (154$mmol.L^{-1}$) is significantly above that of plasma (98-102 $mmol.L^{-1}$). Secondly they lack electrolytes present in the plasma such as potassium, calcium and magnesium. Thirdly, they lack the bicarbonate or bicarbonate-precursor buffer necessary to maintain plasma pH within normal

limits. These factors may be responsible for the homeostatic disruption and the development of metabolic acidosis. [3]

The intra-operative development of metabolic acidosis is frequently attributed to hypovolemia, tissue hypo perfusion, and lactic acidosis. In a prospective, observational study, Waters et al evaluated dilutional acidosis as a possible mechanism for the routine development of intraoperative acidosis in patients undergoing non-cardiovascular surgery. Twelve patients scheduled to undergo surgical procedures expected to last more than 4 hrs were enrolled in the study. Peri-operative management was based on the judgment of the attending anesthesiologist without knowledge of the study's intent. Arterial blood gas parameters, serum electrolytes and urine electrolytes were measured pre- and post-operatively. Pulmonary artery catheters were placed for hemodynamic measurement and oxygen delivery calculations. Plasma volume was measured both pre- and postoperatively, using the Evans blue dye dilution technique. Although significant changes in lactate level (1.1±0.6 to 1.8 ±1.0) occurred, the change was not large enough to explain the change in base excess (0.8±2.3 to -2.7 ±2.9). Chloride levels significantly increased (106 ±3 to 110 ±5) with a significant correlation between the degree of change in chloride to that in base excess. There was a strong correlation between the change in base excess and the volume of normal saline administered and more so the total chloride administered. Classically, 'dilutional acidosis' would explain the predominance of this acidotic change; however, since there was no increase in plasma volume, chloride administration was thought to be the cause of the increase in base deficit. The absence of plasma volume change would suggest that the mechanism postulated to result in dilutional acidosis is incomplete. The common treatment of administering more fluid for intra-operative acidosis may be inappropriate and contribute to the acidosis. The authors suggested that the chloride levels should be assessed whenever a metabolic acidosis is seen peri-operatively. [6]

Potassium containing solutions such as Ringer lactate have been avoided in patient with renal failure with the aim to avoid hyperkalemia. In a prospective randomized double blinded trial O'Malley et al compared the effects of intraoperative administration of normal saline versus ringer lactate in 50 patients undergoing renal transplant. The normal saline group received

6 liters, while the Ringer lactate group received 5.6 liters intraoperatively. Significantly higher number of patients developed hyperkalemia (p=0.05) and metabolic acidosis (p=0.004) in Normal saline group which had to be treated as compared to Ringer lactate group. The study concluded that large volumes of Ringer lactate in patients undergoing renal transplant may be safe and better than normal saline for intravenous fluid therapy. [11]

Correcting the fluid status of the surgical patient is an integral part of good anesthetic practice. Controversies still exist as to what the best solution to give is, whether it be a colloid or a crystalloid, and how and when to give it. There has been an increased awareness about the different properties of colloids and their carrier solution, essentially a choice between saline or Ringer's lactate (compound sodium lactate or Hartmann's solution). Stephens et al have reviewed recent studies involving crystalloids, the 'new colloids' and on the amount and timing of fluid therapy. [24] Saline based fluids (including most colloids) are associated with a hyperchloremic metabolic acidosis and a hypocoagulable state. Saline may have deleterious effects on renal function. Colloids in solutions similar to Ringer's lactate ('balanced solutions') may avoid these effects. The study concluded that compared with Ringer's lactate, saline and saline-based colloids are associated with a hyperchloremic metabolic acidosis and a hypocoagulable state but it may not be associated with adverse patient outcomes. Increasing awareness of the 'Stewart hypothesis' has led to new ways of managing hyperchloremic metabolic acidosis.

Saline-based fluids can have effects on coagulation and urine output in addition to their effects on acid-base balance. [24, 25] Hyperchloremia produces a progressive renal vasoconstriction and fall in glomerular filtration rate that is independent of the renal nerves, is potentiated by prior salt depletion and is related to tubular Cl^- reabsorption. Chloride-induced vasoconstriction appears specific for the renal vessels. [25]

Ringer lactate

The electrolyte content of Ringer lactate solution resembles that of plasma, more closely than 0.9% saline. It is moderately hypotonic, the chloride content is higher and sodium content is lower. The calcium chloride in water dissociates to provide calcium and chloride ions. Approximately 80% of body calcium is excreted in the feces as insoluble salts; urinary excretion accounts for the remaining 20%. Potassium chloride in water dissociates to provide potassium and chloride ions. Potassium is found in low concentration in plasma and the extra-cellular fluids (3.5-5.0mEq.L^{-1}) compared to the intracellular concentration (160mEq.L^{-1}). Sodium chloride in water dissociates to provide Na^+ and Cl^-. Sodium is the principal cation of the extra cellular fluid and plays a large part in the therapy of fluid and electrolyte disturbances. Chloride has an integral role in buffering action when oxygen and carbon dioxide exchange occurs in the red blood cells. Sodium lactate provides sodium and lactate ions. The lactate anion is in equilibrium with pyruvate and has an alkalizing effect resulting from simultaneous removal by the liver of lactate and hydrogen ions. In the liver, lactate is metabolized to glycogen which is ultimately converted to carbon dioxide and water by oxidative metabolism. The Na^+ combines with HCO_3^- produced from carbon dioxide of the body and thus retains bicarbonate to combat metabolic acidosis.

In a double-blind, randomized control trial, Waters et al compared 0.9% saline and Ringer lactate as intraoperative fluid. Thirty-three patients undergoing aortic reconstructive surgery were enrolled and were randomly assigned to receive Ringer lactate or 0.9% saline. Patients receiving 0.9% saline developed hyperchloremic acidosis and needed more bicarbonate therapy (30± 62 ml versus 4 ± 16 ml) which was given if the base deficit was greater than -5 $mEq.L^{-1}$. The normal saline group was associated with significantly more acidosis and received significantly more blood products. They concluded that predominant use of 0.9% saline in major surgery has little impact on outcome as assessed by duration of mechanical ventilation, hospital stay and post-operative complications, but it appear to be associated with increased blood loss during the surgery. [5]

Scheingraber et al, in a dose-response study, randomly assigned 24 patients undergoing major abdominal gynaecological surgery to receive either 0.9% saline or Ringer lactate solution in a dose of $30ml.kg^{-1}.hr^{-1}$. The pH, $PaCO_2$ and serum concentrations of sodium, potassium, chloride, lactate, and total protein were measured in 30 minute intervals. The serum HCO_3 concentration was calculated using the Henderson-Hasselbalch equation and also using the Stewart approach. The strong ion difference was calculated as the difference between the positive (serum Na^+ and K^+) and the negative (serum Cl^{-1} and lactate). The amount of weak plasma acid was calculated as 2.43 times the serum total protein concentration ($g.dL^{-1}$). They found that rapid infusion of 0.9% saline caused a metabolic acidosis with hyperchloremia and a concomitant decrease in the strong ion difference as compared to those who received Ringer lactate. Calculating the serum HCO_3 concentration using the Henderson-Hasselbalch equation or the Stewart approach produced equivalent results. They concluded that infusion of $30ml.kg^{-1}.hr^{-1}$ of 0.9% saline leads to metabolic acidosis, which is not observed with administration of Ringer lactate and the acidosis is associated with hyperchloremia [13]

Takil et al compared the effects of $20ml.kg^{-1}.hr^{-1}$ of 0.9% saline or Ringer lactate on electrolytes and acid-base balance during major spine surgery. Thirty patients aged 18-70 yr were randomly grouped to receive either Ringer lactate or 0.9% saline. General anesthesia was standardized. The electrolytes (Na^+, K^+, Cl^-) and the arterial blood gases were measured pre-operatively, every hour intra-operatively and at the 1st, 2nd, 4th, 6th and 12th hour post-operatively. In the 0.9% saline group, the pH, HCO_3 and base excess decreased and the Cl^- values increased significantly at the 2nd hour and the Na^+ values increased at the 4th hour intra-operatively ($P < 0.001$). The values returned to normal ranges at the 12th hour post-operatively. In the Ringer lactate group, the blood gas and the electrolyte values did not show any significant difference intra-operatively, but the increase in $PaCO_2$, the decrease in pH and serum Na^+ was significant at the 1st hour post-operatively. The study concluded that administration of 0.9% saline leads to hyperchloremic acidosis which was not seen in those who receive Ringer lactate. However, infusion of Ringer lactate leads to post-operative respiratory acidosis and mild hyponatremia.[18]

Plasmalyte 148 / Plasmalyte A

Plasmalyte A is a balanced salt solution with a pH of 7.4. The contents of Plasmalyte A are (in 100ml) 526mg of NaCl, 502 mg of Na gluconate, 368mg of Na acetate trihydrate, 37mg of KCl and 30mg of $MgCl_2$. The pH is adjusted with NaOH. Plasmalyte A produces metabolic alkalinizing effect. The acetate (bicarbonate precursor) and the gluconate ions are metabolized in the liver to CO_2 and water and this reaction requires H^+ ions for its formation. The caloric content is 21 $kcal.L^{-1}$. Plasmalyte A produces a metabolic alkalinizing effect. Plasmalyte 148 differs from Plasmalyte A by having a pH of 5.5.

Lee et al compared the effect of infusing 15 $ml.kg^{-1}.hr^{-1}$ of either 0.9% saline or Plasmalyte 148 on 30 patients undergoing hepato-biliary or pancreatic surgery. The arterial blood gas and the serum biochemistry (Na^+, K^+, Cl^-, lactate) were measured at the beginning, the end and at 24 hrs after the surgery. The patients who received 0.9% saline had a significant increase in chloride levels ($p < 0.01$), decreased standard bicarbonate concentration ($p < 0.01$) and increased base excess ($p < 0.01$) compared to those who received Plasmalyte 148. It was concluded that exclusive use of 0.9% saline intra-operatively can produce temporary hyperchloremic acidosis. It may also exacerbate acidosis resulting from an actual pathological condition. The use of a balanced salt solution such as Plasmalyte 148 may avoid these complications. [4]

Hadimioglu et al in a double-blind study tried to quantify the changes in the acid-base balance, and the levels of potassium and lactate levels caused by the administration of different crystalloid solutions, during kidney transplantation. Patients were randomized to three groups of 30 each, to receive 0.9% saline, Ringer lactate or Plasmalyte, at 20-30 $mL.kg^{-1}.hr^{-1}$. The arterial blood analyses were done before induction of anesthesia and at 30 minute intervals during the surgery. The urine output, the serum creatinine, the BUN and the creatinine clearance were recorded on the 1st, 2nd, 3rd and 7th post-operative days. There was a statistically significant decrease in the pH (7.44 ± 0.50 vs 7.36 ± 0.05) and base excess (0.4 ± 3.1 vs -4.3 ± 2.1) and a significant increase in serum Cl^- (104 ± 2 vs 125 ± 3 $mEq.L^{-1}$) in patients who received 0.9% saline. The lactate levels increased significantly in patients who received Ringer lactate (0.48 ± 0.29 vs 1.95 ± 0.48). There was no significant change in the acid-base measures or the lactate levels in patients who received Plasmalyte. The potassium levels did not show any significant change in any group. They concluded that all three crystalloid solutions can be safely used during uncomplicated, short-duration renal transplants; however, the best metabolic profile is maintained in patients who receive Plasmalyte [7].

Restricted Vs Liberal fluid regime

Branstrup et al in a randomized assessor-blinded multicentric trial studied the effects of intravenous fluid restriction on post operative complications after colorectal surgery. One hundred and seventy two patients were allocated to receive either a restricted or a standard intra-operative and postoperative fluid regime. The ‘standard’ fluid regime consisted of preloading with colloid, replacing third space loss and loss during fasting with crystalloids. In the ‘restricted’ regime there was no preloading or replacement of lost fluid due to fasting or third space loss. Blood loss upto

1500 ml was replaced with crystalloids/colloid and above that with blood. The restricted regime aimed at maintaining preoperative body weight. The primary out-come measured were complications like anastomotic leak, peritonitis, wound dehiscence, bleeding, and intestinal obstruction. The secondary outcome measured death and adverse effects. The restricted fluid regimen significantly reduced the postoperative complications both by intention-to-treat (33% versus 51%, p- 0.013) and per-protocol (30% versus 56%, p- 0.003) analyses. The numbers of both cardiopulmonary (7% versus 24%, p- 0.007) and tissue-healing complications (16% versus 31%, p- 0.04) were significantly reduced. No patients died in the restricted group compared with 4 deaths in the standard group (0% versus 4.7%, p- 0.12). The study concluded that the restrictive peri-operative fluid regime reduces complications significantly. [26]

Kita T et al. studied 112 patients, undergoing trans-thoracic esophagectomy for carcinoma. They observed the incidence of post-operative pulmonary complications in these patients, when a restricted fluid regime was given and compared it to a historical group in whom intra-operative fluids were administered liberally. The fluid was administered at 4-5 $ml.kg^{-1}.hr^{-1}$ and the CVP maintained <5 mm Hg. The initial blood loss was replaced with crystalloids or colloid until the fall in hematocrit was less than or equal to 25 %. Blood was transfused if hematocrit fell below 25%. The intra-operative volume balance decreased more so in the late period compared with early period ($p < 0.0001$). The need for tracheostomy, bronchoscopic suctioning, and extubation failure on 1st post-operative day were significantly more frequent in the early period than in the late period (p- 0.0083, p- 0.0319, and p- 0.0024, respectively). The hospital recovery period after surgery was shortened during the late period (p- 0.032). Intra-operative volume balance affected the need for tracheostomy and frequent bronchoscopy post-operatively. The author concluded that restricted intra-operative fluid administration reduces post-operative pulmonary complication and shortens recovery time. [9]

Determining adequate fluid volume resuscitation is a major clinical challenge. It is not uncommon for patients undergoing major surgical procedures to gain 5-10 kg in weight as a result of positive fluid balance. [10] Positive salt and water balance, sufficient to cause a 3 kg weight gain after surgery delays return of gastrointestinal function and prolongs stay in patients undergoing colonic surgery. [10]

Nisanevich et al studied the impact of two intraoperative fluid regimes on post-operative outcome in 152, ASA grade I-III, patients who underwent elective intra-abdominal surgery. Patients were randomly assigned to receive either liberal (liberal protocol group [LPG], n = 75); bolus of 10 $ml.kg^{-1}$ followed by 12 $ml.kg^{-1}hr^{-1}$, or restrictive fluid regime (restrictive protocol group [RPG], n = 77), 4 $ml.kg^{-1}hr^{-1}$ of Ringer lactate, intra-operatively. The primary endpoint was the number of patients who died or experienced complications. The secondary endpoints included time to initial passage of flatus and feces, duration of hospital stay, and changes in body weight, hematocrit, and albumin serum concentration in the first 3 postoperative days. Analysis showed that number of patients with complications were lower in the RPG ($P = 0.046$). Patients in the LPG passed flatus and feces significantly later (flatus, median (range): 4 (3-7) days in the LPG vs. 3 (2-7) days in the RPG; $p< 0.001$; feces: 6 (4-9) days in the LPG vs. 4 (3-9) days in the RPG; $p< 0.001$), and their post-operative hospital stay was significantly longer (9 (7-24) days in the LPG vs. 8 (6-21) days in the RPG; p- 0.01). Significantly larger increases in body weight were observed in the LPG compared with the RPG ($p< 0.01$). In the first 3 postoperative days, hematocrit and albumin concentrations were significantly higher in the RPG compared with the LPG. The study concluded that of intra-operative restrictive fluid management may be advantageous in patients undergoing elective intra-abdominal surgery, because it reduces postoperative morbidity and shortens hospital stay. [15]

'Goal-directed' intra-operative fluid

It is suggested that goal-directed fluid therapy may allow individualized fluid therapy that adapts to changing patient needs during the perioperative period and prevents subtle hypovolemia or hypervolemia. Goal-directed therapy uses the concept of fluid challenge to optimize the predetermined goal. Individualized goal-directed fluid optimization facilitates early recovery and reduces hospital stay. [21]

Fasting, anesthesia and surgery affect the body's physiological capacity to control its external fluid and electrolyte balance. Abnormalities of fluid and electrolyte balance may adversely affect organ function and surgical outcome. Perioperative fluid therapy has a direct bearing on outcome of the patient's condition. The goal of fluid therapy in the elective setting is to maintain the effective circulatory volume while avoiding interstitial fluid overload whenever possible. Weight gain in elective surgical patients should be minimized in an attempt to achieve a 'zero fluid balance status. Patients should arrive in the theatre room in a state of normal fluid and electrolyte balance so as to avoid the need to resuscitate fluid-depleted patients. Optimal fluid delivery should involve preoperative fasting, adequate fluid administration and analgesia, avoidance of nasogastric tubes, early mobilization, and early return to oral feeding, as exemplified by the enhanced recovery after surgery programme. [23]

In a prospective, randomized study the effect of goal-directed intra-operative fluid administration was studied on duration of post-operative hospital stay. One hundred patients who were scheduled to undergo major elective surgery with an anticipated blood loss greater than 500 ml were randomly assigned to a control group (n= 50) that received standard intra-operative care or to a protocol group (n= 50) that, in addition, received intra-operative plasma volume expansion guided by the esophageal Doppler monitor to maintain maximal stroke volume. Length of post-operative hospital stay and post-operative surgical morbidity were assessed. The protocol group had a significantly higher stroke volume and cardiac output at the end of surgery compared with the control group. Patients in the protocol group had a shorter duration of hospital stay compared with the control group: 5 ± 3 versus 7 ± 3 days, with a median of 6 versus 7 days, respectively (p- 0.03). These patients also tolerated oral intake of solid food earlier than the control group: 3 ± 0.5 versus 4.7 ± 0.5 days, with a median of 3 versus 5 days, respectively (p- 0.01). Therefore, 'goal-directed' intra-operative fluid administration results in earlier return to bowel function, lower incidence of postoperative nausea and vomiting, and decrease in length of postoperative hospital stay.[16]

<u>Acid-Base - Stewart approach</u>

Stewart theory rests on two important physicochemical principles:

1. The law of electro-neutrality – In a solution, the number of positively charged ions must be equal to the number of negatively charged ions.
2. The law of conservation of mass - The total amount of a substance remains constant, unless it is added to or generated, or removed or destroyed.[3]

Stewart concluded that one might model acid-base disturbances, based on the three conceptual contributors,

1- Strong Ion difference (SID)

2- Weak Acids in Plasma (A)

3- PCO_2.

According to the law of electrical neutrality:

$$[Na^+] + [K^+] + [H^+] = [Cl^-] + [lactate^-] + [HCO_3^-] + [A^-] + [CO_3^{2-}]$$

Ignoring the minimal contribution of $[H^+]$, $[HCO_3^-]$ and $[CO_3^{2-}]$:

$$[SID] = [HCO_3^-] + [A^-]$$

Stewart puts the three variables together in the Stewart Equation described in the equation box. If contribution of albumin is ignored in this equation, it simplifies to the Henderson-Hasselbalch equation. Thus, albumin is the major variable that Stewart has added in, left out by Siggaard-Andersson for reasons of simplicity

Stewart originally described the equation as follows:

$$SID = (Na^+ + K^+) – (Cl^- + Lactate) \sim 40\text{-}49 \text{ mEq.L}^{-1}$$

Lactate

One of the best indicators currently available to assess the adequacy of oxygen delivery in the critically ill patient is the blood lactate concentration. During tissue hypoperfusion and hypoxia, anaerobic metabolism occurs and pyruvate generated by glycolysis is converted to lactate and is often measurable as an increase in the circulating lactate concentration. [20]. The severity of lactic acidosis in critically ill patients correlates with overall oxygen debt and survival. Lactate determinations may be useful as an ongoing monitor of perfusion as resuscitation proceeds. Therapy of critically ill patients with lactic acidosis is designed to maximize oxygen delivery in order to reduce tissue hypoxia by increasing cardiac index, while maintaining hemoglobin concentration. Buffering agents have not been shown to materially affect outcome from lactic acidosis caused by shock. [21]

Methodology

The study protocol was approved by the institutional review board, prior to the commencement of the clinical trial. The study was explained to all the patients and an informed consent was obtained from each patient who volunteered. Sixty, ASA (American Society of Anesthesiologists) grade I or II, patients scheduled for upper abdominal surgery were enrolled and randomly allocated to one of the two groups.

Group A - Plasmalyte A

Group B - Ringer lactate

Anesthetic Technique

The anesthetic technique was standardized in all the patients. General anesthesia was induced with thiopentone-vecuronium-fentanyl and maintained with O_2-air-isoflurane. The peri-operative monitoring of the patient included electrocardiogram (ECG), Pulse oximetry (SpO2), non-invasive blood pressure (NIBP), central venous pressure (CVP), end-tidal carbon-dioxide ($ETCO_2$), urine output and nasopharyngeal temperature.

Study intervention

When the patient arrived inside the operating room, the randomization envelope, as per the serial number, was opened and the patient was allotted to either Group I (Plasmalyte A) or Group II (Ringer lactate). The allotted bag of fluid was wrapped within an opaque cover, so as to blind the anesthesiologist of the type of fluid. The study fluid was infused at **5-7 $ml.kg^{-1}.hr^{-1}$**. The aim was to maintain the CVP at 5 mm Hg. If it was not achieved with the use of the study fluid a bolus of 100ml of a colloid, tetra-starch (Voluven ®) was administered. An arterial blood sample was taken after induction of anesthesia and at the end of the surgery to measure the arterial blood gas and the serum electrolytes (sodium, potassium, chloride and lactate).

Sample size calculation

The sample size was calculated based on two similar studies [4, 5] using the 'two sample mean comparison' method.

Lee et al [4] compared the effect of Plasmalyte 148 with 0.9% saline, administered at the rate of 15ml.kg^{-1}.hr^{-1} as intraoperative maintenance fluid. The post-operative base excess was significantly lower in patients who received 0.9% saline (-5.0 ±2.1) as compared to those who received Plasmalyte 148 (-1.2 ±1.1).

Similarly, Waters et al [5] compared Ringer lactate and 0.9% saline and demonstrated that the post-operative base excess was significantly lower in those who received 0.9% saline (-3.8 ±3.9) compared to those who received Ringer lactate (-2.2 ± 2.0).

The sample size was calculated using the formula:

$$\mathbf{n = \frac{(Z\,\alpha/2 + Z\,1-\beta)^2 \times 2 \times S^2}{D^2}}$$

S = Average of the two standard deviations

D = Difference in the means

$Z\,\alpha/2$ = 1.96 (5% LEVEL OF SIGNIFICANCE)

$Z\,1-\beta$ = (80% POWER) =0.842.

Since this study was to compare Plasmalyte A and Ringer lactate, the post-operative base excess values (mean and standard deviation) of Plasmalyte 148 and Ringer lactate from the two studies were taken. However, since Plasmalyte A has a pH of 7.4 compared to 5.5 of Plasmalyte 148, the difference in mean was taken as 1.2 instead of 1 and the average standard deviation as 1.6. Substituting these values into the formula gave a sample size of 27 in each arm. It was decided to study 30 patients in each group.

Randomization and Blinding

A computer-generated randomization table was drawn up in blocks of ten. The name of the study fluid to be used (Plasmalyte A or Ringer lactate) was written on a piece of paper and enclosed in serially numbered envelopes. When the enrolled patient arrived in the operating room the envelope, as per the serial number, was opened by a person not involved in the study. The correct fluid was then connected to the administration set and the bag was wrapped with an opaque cover so as to blind the investigating anesthesiologist.

Statistical Analysis

The basic structure of the analysis was a comparison of two groups of patients. The primary aim was to detect any post-operative change in the acid-base status of these patients. The analysis was done using ‘SPSS for Windows’ version11 software. The mean and the standard deviation of the pre- and the post- operative measured parameters were calculated and the test of significance was applied. The post-operative values were independently subjected to t-test for change.

Results

Sixty, ASA grade I or II, patients scheduled for major abdominal surgery, were randomly allocated to either Group 1 (Plasmalyte A) or Group 2 (Ringer lactate). The demographic characteristics of the patients were comparable between the two groups (Table 1). The type of surgery and the duration of surgery were also similar. There was no statistically significant difference in the volume of study crystalloid administered between the two groups. None of the patients had any significant complications during or immediately after the surgery.

Table 1 Patient characteristics and operative details.

		(Group 1) Plasmalyte A n=30	(Group 2) Ringer lactate n=30	p-value
Age (yr)		47.8 ± 10.23	47.7 ± 13.87	0.95
Weight (kg)		54.7 ± 12.11	51.2 ± 7.89	0.19
Duration (hrs)		4.43 ± 1.35	4.43 ± 1.16	0.43
Blood loss (ml)		293.33 ± 218.8	314 ± 247	0.73
Crystalloid infused	mL	1432.4 ± 554.9	1316 ± 430.7	0.37
	$ml.kg^{-1}.hr^{-1}$	5.9	5.8	
Colloid infused		331 ± 322.2	430 ± 358	0.68
Type of surgery				
Total gastrectomy		10	11	
Subtotal gastrectomy		7	6	
Choledochol cyst		8	7	
Hepaticojejunostomy		3	4	
Triple bypass		2	2	
Post-operative stay (days)		8.7 ± 3.6	9.9 ± 3.9	0.22

The serum electrolytes and the arterial blood gas analyses were done in all the patients before and after the surgery. There was not statistically significant difference between the two groups with regard to the pre-operative and the post-operative values of serum electrolyte, arterial acid-base status. (Table 2 & 3)

Table 2: **Pre-operative** values of serum electrolytes and arterial blood gases

	(Group 1) Plasmalyte A n=30	**(Group 2) Ringer lactate n=30**	p-value
Sodium	139.33 ± 2.97	134.23 ± 3.4	0.24
Potassium	3.65 ± 0.39	3.71 ± 0.29	0.48
Chloride	103.83 ± 3.79	103.73 ± 5.07	0.93
pH	7.40 ± 0.46	7.41 ± 0.04	0.27
Bicarbonate	21.91 ± 1.96	22.32 ± 3.07	0.53
Base excess	-1.74 ± 2.25	-1.0 ± 3.59	0.36
Arterial CO_2	34.90 ± 4.06	34.91 ± 5.23	0.99
Lactate	1.28 ± 0.50	1.43 ± 0.57	0.31

Table 3. **Post-operative** values of Serum electrolyte and arterial blood gas

	(Group 1) Plasmalyte A n=30	**(Group 2) Ringer lactate n=30**	p-value
Sodium	138.43 ± 3.26	137.7 ± 3.70	0.46
Potassium	3.71 ± 0.28	3.86 ± 0.50	0.15

Chloride	104.3 ± 4.55	105.67 ± 4.86	0.26
pH	7.33 ± 0.05	7.31 ± 0.06	0.20
Bicarbonate	20.31 ± 2.29	20.29 ± 2.83	0.96
Base excess	-4.38 ± 2.61	-3.77 ± 3.38	0.43
Arterial CO2	38.69 ± 5.37	38.38 ± 6.68	0.84
Lactate	2.48 ± 1.20	2.90 ± 1.51	0.24

The groups were analyzed to assess if the administration of either Plasmalyte A or Ringer lactate resulted in any change in the measured value, within the group. (Table 4 & 5)

In both the groups, there was no significant difference between the pre-operative and the post-operative electrolyte values. However, there was significant decrease in the pH in the post-operative blood gases compared to the pre-operative values, in both the groups. This acidosis was not clinically significant. The development of acidosis seems to be contributed by increase in arterial CO_2 levels as well as reduction in serum bicarbonate levels. The level of lactate was also significantly increased in both the groups.

Table 4: Group A- Plasmalyte A (n=30)

	Preoperative	Postoperative	Difference	p-value
Sodium	139.33 ± 2.97	138.43 ± 3.26	0.90 ± 2.60	0.68
Potassium	3.65 ± 0.39	3.71 ± 0.28	-0.05 ± 0.51	0.54
Chloride	103.83 ± 3.79	104.3 ± 4.55	-0.47 ± 4.71	0.59
pH	7.40 ±0.46	7.33 ± 0.05	0.06 ± 0.06	**0.000**

Bicarbonate	21.91 ± 1.96	20.31 ± 2.29	-1.60 ± 2.36	**0.001**
Base excess	-1.74 ±2.25	-4.38 ± 2.61	2.63 ± 2.97	**0.000**
Arterial CO_2	34.90 ± 4.06	38.69 ±5.37	-3.79 ± 5.94	**0.002**
Lactate	1.28 ± 0.50	2.48 ±1.20	-1.20 ± 0.95	**0.000**

Table 5: Group B- Ringer lactate (n=30)

	Preoperative	Postoperative	Difference	p-value
Sodium	134.23 ± 3.4	137.77 ± 3.70	-3.53 ± 4.03	0.42
Potassium	3.71 ± 0.29	3.86 ± 0.50	-0.14 ± 0.48	0.10
Chloride	103.73 ± 5.07	105.67 ± 4.86	-1.93 ± 9.47	0.69
pH	7.41 ± 0.04	7.31 ± 0.06	0.09 ± 0.05	**0.00**
Std HCO_3	22.32 ±3.07	20.29 ± 2.83	2.03 ± 3.87	**0.05**
Base excess	-1.0 ± 3.59	-3.77 ± 3.38	2.73 ± 4.02	**0.00**
Arterial CO_2	34.91 ± 5.23	38.38 ± 6.68	-3.47 ± 11.23	**0.03**
Lactate	1.43 ± 0.57	2.90 ± 1.51	-1.47 ± 1.40	**0.00**

The changes caused in each group were compared as shown in Table 6. The decrease in pH was significantly more among those who received Ringer lactate as compared to that seen among those who received Plasmalyte A.

Table 6: Student t – test for change

	(Group 1) **Plasmalyte A** **n=30**	**(Group 2)** **Ringer lactate** **n=30**	p-value
Sodium	0.90 ±2.60	-3.53 ± 4.03	0.31
Potassium	-0.05 ±0.51	-0.14 ± 0.48	0.48
Chloride	-0.47 ± 4.71	-1.93 ± 4.10	0.20
pH	0.06 ± 0.06	0.09 ± 0.05	**0.03***
Bicarbonate	1.60 ± 2.36	2.03 ± 3.87	0.53
Base excess	2.63 ± 2.97	2.73 ± 4.02	0.91
Arterial CO_2	-3.79 ± 5.94	-3.47 ± 7.95	0.86
Lactate	-1.20 ± 0.91	-1.47 ± 1.40	0.37

Discussion

The aim of this study was to compare the electrolyte levels and the acid-base status in patients receiving either Plasmalyte A or Ringer lactate as maintenance fluid, during major abdominal surgery. This double-blind, randomized trial has demonstrated that administration of 5-7 $ml.kg^{-1}.hr^{-1}$ of either of these fluids does not change the electrolytes significantly. However, this volume of fluid reduces the pH which, although not clinically significant, is statistically more with the use of Ringer lactate. The decrease in pH seems to be contributed by increase in arterial CO_2 as well as decrease in serum bicarbonate.

0.9% 'normal' saline has been used as intra-operative fluid therapy and for a multitude of clinical conditions including trauma and diabetic ketoacidosis. Yet, it is neither 'normal' nor physiological [3]. Hyperchloremic acidosis is now a well accepted entity observed after infusion of large volumes of 0.9% saline. [4, 5, 6, 8, 14, 11, 19] This is attributed to dilution of plasma by large volume of fluid with high chloride content and deprived of bicarbonate or its precursor. However, this explanation is not convincing since studies have shown high levels of chloride without change in plasma volume. According to the Stewart hypothesis, infusion of large quantity of Cl^- reduces the strong ion difference leading to acidosis. This has lead to the use of balanced salt solutions such as Ringer lactate and Plasmalyte. Several studies have shown that the use of 0.9% saline significantly increases the acidosis and chloride level as compared to when Ringer lactate or Plasmalyte is used [4, 5, 6, 11, 19]. Although, these studies have shown that the effect of the balanced salt solutions on acidosis is minimal, there are none that have compared the two balanced salt solutions in patients undergoing major abdominal surgery.

Most studies have looked into the effect of transfusing large volumes of crystalloids (15-30 $ml.kg^{-1}.hr^{-1}$) and demonstrated significant effect on the electrolytes and the acid-base status. However, it is well accepted now that fluid restriction reduces the incidence of peri-operative complications such as cardiopulmonary events and impaired bowel motility, while improving wound and anastomotic healing. In this study, the volume of fluid infused was 5-7 $ml.kg^{-1}.hr^{-1}$, based on the various studies which recommend 'restricted' fluid regime [9,10,15,26]. The central venous pressure was measured and maintained at 5 mmHg, with boluses of tetrastarch.

The lactate levels in both the groups had significantly increased, albeit within normal limits. Although, infusion of large volume of Ringer lactate is known to increase lactate levels, [7] rising serum lactate is generally associated with tissue hypoperfusion. During tissue hypoperfusion and hypoxia, the pyruvate generated by glycolysis is converted to lactate by anaerobic metabolism. [20]. It could be argued that it may be that the volume of fluid infused (5-7ml.kg^{-1}.hr^{-1}) was relatively low as evidenced by the fact that 1-2 ml.kg^{-1}.hr^{-1} of colloid was needed to maintain the CVP at 5 mmHg. However, the volume of colloid infused matched the calculated volume of blood loss.

The acidosis caused by 0.9% saline is attributed to the dilution of bicarbonate and the infusion of high concentration of Cl^-. According to Stewart's hypothesis, the reduction in strong ion difference (SID = Sodium + Potassium – Chloride – lactate) is associated with rise in H^+ leading to acidosis. SID can also be affected by the presence of weak organic acids such as lactate and possibly (?) acetate. Since these negatively charged molecules reduce the SID they lead to acidosis. In this study, although, the pH was decreased marginally more in the Ringer lactate group the reduction in SID was slightly more in group A (37.9 to 35.4) as compared to no change in group B (32.8). Could this have been due to the unmeasured acetate?

In the liver, lactate is metabolized to glycogen which is ultimately converted to carbon dioxide and water by oxidative metabolism. The CO_2 and water produces bicarbonate. Acetate is also metabolized to produce bicarbonate. The acetate-containing solutions have at least a theoretical advantage over lactated solutions, since the capacity to metabolize lactate is mainly in the liver and kidney, while acetate can be metabolized in all tissues, which could be beneficial in patients who are hypovolemic or in shock. [27]

The shortcomings of this study include some unanswered questions:

1. Does 0.9% saline infused in the dose of 5-7 $ml.kg^{-1}.hr^{-1}$ cause any electrolyte and acid-base abnormality?

If a third 'control' group, that could be randomized to receive the same volume of 0.9% saline, was included in the study, it would have answered this query and also how it compares to that seen with Ringer lactate or Plasmalyte A.

2. Could infusion of a larger volume have prevented the rise in lactate levels?

The administration of the saline-based colloid to maintain the CVP at 5 mmHg would have also contributed to the acidosis. This could have been avoided if the study fluids were administered at about 10 $ml.kg^{-1}.hr^{-1}$.

Conclusion

The choice of the intravenous fluid during surgery is often assumed to be of little significance. However, the widely used 0.9% saline has been shown to cause significant acidosis when compared to balanced salt solutions such as Ringer lactate or Plasmalyte. This study was an effort to compare the effect of administering lactate-based and acetate-based intravenous fluids on the electrolytes and the acid-base status.

This double-blind randomized control study was approved by the Institutional Review Board and all the patients enrolled signed an informed consent. Sixty, ASA grade I or II, patients scheduled for major abdominal surgery, were randomly assigned to receive either Ringer lactate or Plasmalyte A at the rate of 5-7 $ml.kg^{-1}.hr^{-1}$. The arterial blood gas analysis and the electrolytes were measured before and at the end of surgery.

The patient characteristics were comparable between the two groups. The pre-operative and the post-operative electrolyte levels showed no significant difference in either group. However, when the pre-operative and post-operative values were compared, there was statistically significant decrease in pH in both the groups, with it being marginally more among those who received Ringer lactate. There was both a slight rise in $PaCO_2$ as well as a slight decrease in bicarbonate. However, the post-operative pH was within normal limits and was not clinically significant.

This study concludes that in patients undergoing major abdominal surgery, the administration of 5-7 $ml.kg^{-1}.hr^{-1}$ of either Plasmalyte A or Ringer lactate leads to statistically significant decrease in pH, but this change is not clinically significant. However, when the two groups are compared, there is no statistically significant difference in the electrolyte and the acid-base status.

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INFORMED CONSENT DOCUMENT

PATIENT INFORMATION:

0.9% saline and Ringer lactate are the most widely used intravenous fluids used in our hospital. It has been shown that both these fluid can contribute to metabolic acidosis when used in large amounts, with it being more with 0.9% saline. A new balanced solution, Plasmalyte A is now available which has a pH similar to that of blood, and is thought to contribute very minimal to acidosis with its use.
In this study we want to compare the effect of either Ringer lactate of Plasmalyte A on the acidosis and the electrolytes.
If you volunteer for this study, you will be randomly assigned to receive either Plasmalyte A or Ringer lactate. Two samples of blood (6 ml each) will be drawn, while you are asleep, before the start and at the end of surgery.
The participation in this study is entirely voluntary, and the care you receive will be the same whether you volunteer or not.

CONSENT

I have been explained the study protocol, by Dr. ________________________in detail, in the language I understand. I am willing to volunteer for this study out of my own free will and am aware that I can withdraw from the study at any time, without it in anyway affecting the treatment I receive in this hospital.

Patient's Signature--____________________

Signature of principal investigator - ____________________

Performa _S.No-

Name Age Weight _
Hospital no
Diagnosis

Procedure –

	preoperative	postoperative
pH		
PaCO2		
PaO_2		
HCO_3		
ABE		
Na		
K		
Cl		
Lactate		

Duration- blood loss- urine output-

Fluid administered-

Crystalloid - colloid - blood - blood products -

Patient transferred to - ward/shdu/sicu.

Indication for transfer to shdu/sicu -